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MEDICAL RESEARCH AT YALE IN THE TWENTIETH CENTURY†

PREPARATORY EVENTS

To understand the conditions that made possible the great development of research at Yale within the past 50 years we must inevitably look into the preceding century. There were external influences. The fire of European science was burning at its brightest, fed by such men as Ludwig, Pasteur, Virchow, and Cohnheim. William Henry Welch was the Prometheus of American medicine who bore the sacred flame to the newly founded Johns Hopkins Hospital and Medical School. It is of interest here that both he and Daniel Coit Gilman, the President of the new University in Baltimore, were graduates of Yale, and the former repeatedly gave invaluable stimulus and assistance to the then struggling medical school of his alma mater. In a commencement address at Yale as early as 1888 he put it thus: "In no other direction could this University expand with greater promise of usefulness and of renown than in the line of liberal support of the highest and most scientific medical education."

By the 1870's conditions in New Haven were indeed becoming more favorable for the development of the biological sciences. Timothy Dwight, while still a Professor in the Theological Department and before he had become a great President of Yale, pronounced the worth and unity in scholarship of all University disciplines including medicine. He extolled the benefits to be obtained from a full-time system in the medical school—that was then 40 years in the future. In that decade the Sheffield Scientific School began to function actively. In 1874, while an undergraduate just 18 years old, Russell H. Chittenden was chosen to be director of a laboratory of physiological chemistry, and in 1880 he received the first Ph.D. to be awarded in that subject in America. He had proceeded to educate himself in the laboratory of Professor Kühne in Germany, with whom he subsequently maintained a scientific collaboration, and in 1882 he was appointed Professor of Physiological Chemistry in the first great laboratory devoted to that science in this country.

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† Presented at the Sesquicentennial Anniversary Program of the Yale University School of Medicine.

It was in the first 20 years of the present century that two great deans transformed the Yale Medical School into a center of research. During the tenure of Dean George Blumer the interest of the University authorities was aroused so that, with the help of the General Education Board, the full-time system for clinical as well as basic sciences was introduced and an effective working relationship with the New Haven Hospital was established making clinical research possible. His dynamic successor Dean Winternitz, with the full support of President James Rowland Angell, was able to assemble a faculty of superb investigators and teachers while stimulating munificent donations from the Rockefeller Foundation, General Education Board, and Commonwealth Fund. The new donations made possible the construction of the first great plant of the school of medicine. Both deans were Hopkins trained. Thus, in the words of John Fulton, "the Hopkins discharged the debt it owed to Yale."

Professor Chittenden's laboratory was the intellectual birthplace of two others of the first great group of experimental biological scientists to teach at Yale, Profs. Lafayette B. Mendel and Yandell Henderson. These men were soon joined by Ross Granville Harrison, a Hopkins graduate, as Professor of Biology, and Harrison made discoveries of the first scientific magnitude. In providing proof that nerve fibers are an outgrowth of nerve cells he devised the method of tissue culture for animal cells. This method has ultimately led to such achievements as the development of the Salk vaccine. Professor Mendel continued in biochemistry at Yale pursuing the great tradition that has been maintained to the present day. Henderson acquired international stature as a physiologist as a result of his work on the physiology of respiration.

STUDIES OF THE "HIDDEN HUNGER"

With Chittenden, Mendel became one of the founders of the science of nutrition. The former had done pioneer work on enzymes in digestion, and considered as his greatest achievement the establishment of the protein requirements of man. Mendel, in collaboration with Dr. Thomas Burr Osborn of the Connecticut Agricultural Experiment Station, made the fundamental discovery that some proteins were nutritionally inadequate since they lacked amino acids that could not be synthesized by the body. These he christened "essential" amino acids. He was also a pioneer in this country in the discovery of vitamins, "substances which do not fulfill their physiological mission because of the energy which they supply." As early as 1910 he found an important growth factor in milk residue, which contained water soluble substances later known as "vitamin B." These were extensively

investigated by Dr. Cowgill. Three years later he discovered that a serious eye disease, xerophthalmia, developed in rats lacking the fat soluble vitamin A. Professor Underhill called attention to production in dogs of a pathological condition closely resembling human pellagra. Subsequent studies on vitamin deficiencies were conducted by Drs. Yudkin, Lambert, Tyson, and Smith. Important work on the effects of vitamin deficiencies on the nervous system was done by Dr. Harry Zimmerman and associates.

PROTEIN STRUCTURE

Recently knowledge of those remarkable biological catalysts, the enzymes, was notably advanced by the studies of proteinases by Professor Fruton and associates, and more specifically the discovery of transpeptidation whereby certain radicals can be replaced. This enzymatic mechanism explains in part the method whereby complex specific protein molecules can be created under physiological conditions by the elongation of peptide chains which are their building blocks. The first demonstration of the net biosynthesis of a discrete protein (cytochrome-C) in subcellular particles was by Dr. Simpson in 1958.

The means whereby the heart of the cell, the nucleus, is constructed has been under intensive investigation. Dr. Charles Carter's discovery that adenylosuccinic acid is an intermediate in nucleic acid metabolism is an important contribution. The structural basis of ribonuclease activity has been investigated by Dr. Richards. Dr. Welch and his active group have used chemically modified building blocks such as 5-iododeoxyuridine in the hope that these would be incorporated into nuclei, thereby impairing growth and possibly controlling tumors. At least partial success has been attained, thereby opening another front in the effort against neoplastic disease.

CHEMISTRY AT THE BEDSIDE

It has been asked: "What are thou life?" and answered: "A thing of watery salt held in suspension by a slime." At Yale the salt and water and the jelly of life have indeed been well studied. Brilliant work by Prof. Frank Pell Underhill during World War I brought out that both in war gas poisoning and in burns there were profound upsets in the water and salt metabolism of the body. Restoration of hydration and of salt balance produced a striking improvement. With the arrival of Dr. John Punnett Peters in New Haven, chemistry was more and more brought to the bedside. His masterpiece, the two-volume *Clinical chemistry* written with Dr. Donald D. VanSlyke, made the knowledge generally available. Dr. Peters became surrounded by eager and brilliant students who today comprise the Who's Who

of metabolic disease—Danowski, Epstein, Elkinton, Welt, and Max Miller, to mention but a few. Diabetes was shown to be, in fact, a state of starvation and that additional protein and sugar were needed to make up for the losses in that chronic disease. Later another sugar, fructose, was found to be better tolerated in this disease, as previously reported, and its study contributed knowledge of the nature of diabetes itself. In uncontrolled diabetes, diabetic acidosis, a state of shock was found to result from loss of salt and appropriate therapeutic measures were instituted. For many years Dr. Peters was the faithful head of a "Diabetic Acidosis Team" that day and night would attend these acute medical emergencies. The rapid intravenous glucose tolerance test for diabetes was introduced in the early forties and this has gained wide acceptance as a standard.

Fundamental additions to knowledge of carbohydrate metabolism were made in the late twenties and early thirties by Drs. Himwich and Nahum and associates. The glucose-lactic acid cycle involving muscle and liver were elucidated, and the respiratory quotients of many organs including brain were worked out.

The movement of water and salt within the body and its derangement in such other diseases as nephritis were an important preoccupation of the Peters group from which came noteworthy advances in the understanding and treatment of disease. Dr. Man, in collaboration with Dr. Peters and more recently with Dr. Margaret Albrink, has contributed to the study of blood lipids in diabetes, renal, thyroid, and other diseases. The problem of the blood fats has assumed a new interest in relation to coronary disease. Within the past three years a new era in the study of lipid metabolism was opened by Dr. S. R. Lipsky's adaptation of gas chromatography. Thanks to his work analytical micromethods for various fats are available and many critical separations can be accomplished for the first time.

In the Department of Pediatrics, a parallel effort has been directed at the metabolic problems peculiar to children by Dr. Daniel Darrow and such brilliant co-workers as Harold E. Harrison and Robert E. Cooke. Perhaps the most valuable and widely acknowledged contribution is the recognition that the loss of precious salts, especially potassium, from the body fluids, rather than the action of a toxin, is largely responsible for the profound consequences of diarrhea, especially in infants. Again replacement therapy proved the clue to success in treatment.

The presence of profound metabolic upsets in surgical patients has become increasingly apparent. Endocrine mechanisms, with special reference to thyroid-adrenal interrelationships, have been under investigation by Drs. Hayes and Goldenberg.

YALE AND HORMONES

The work of many investigators in several departments has made Yale an outstanding center of research on hormones. When Dr. Edgar Allen came to New Haven in the early thirties he brought with him from the University of Missouri an active group of younger men including Drs. Gardner, Diddle, and Burford, each of whom has gained distinction in his own right. Previous studies on the sex hormones were continued. They arrived at the estrogen-withdrawal hypothesis of menstruation which is now generally accepted. Estrogen, the female sex hormone prevents the onset of uterine bleeding; on withdrawal, menstruation is precipitated. Furthermore, this group found that these hormones possess the remarkable property of stimulating the growth of various organs and tissues, and of greatest interest, perhaps, that they could induce or otherwise affect the development of tumors. Drs. Hooker and Forbes made an important contribution in devising a test for one of these substances, progesterone.

Another substance, prolactin, concerned in the control of the secretion of milk, was prepared in highly purified crystalline form by Drs. White, Bonsnes, and Long. In 1940 Drs. Fry, Long, and Katzin demonstrated that adrenal steroids of the type of cortisone control the rate of gluconeogenesis, sugar formation from protein—an effect probably responsible for the therapeutic action of these agents in many types of disease. White and Dougherty made the interesting disclosure that cortisone reduced the number of circulating white blood cells—which led to the use of the substances in controlling certain forms of leukemia.

The first highly purified and potent preparations of ACTH, the pituitary hormone that acts as a whip to the adrenals, were isolated by Drs. Sayers, White, and Long in 1943. With these purified preparations it became possible for members of the group to show that this hormone specifically depletes the adrenal of cholesterol and ascorbic acid. This has been used throughout the world as a method for assaying ACTH or demonstrating its release in the body. In the years 1947-1950 Drs. Fry, Gershberg, McDermott, and Long demonstrated that epinephrine stimulated the release of ACTH. They were the first to point out that the secretion of ACTH was controlled by a dual mechanism, the first related to the activity of the hypothalamus and the second probably related to the level of adrenal steroids in the blood. These studies are being continued by Dr. Brodish. Another feat of purification of a highly important biological substance was that of Drs. Wilhelmi, Fishman, and Jane Russell who in 1948 succeeded for the first time in crystallizing growth hormone. Their method has now become the standard.

Shortly before coming to Yale, Dr. Lerner discovered that the pituitary contained a skin darkening hormone now known as melanocyte stimulating hormone (MSH). The chemical structure of hog alpha-MSH was determined by this able investigator and most of the chemical structure of human ACTH was established. Recently, a skin-lightening hormone, christened Melatonin effective in frog skin was discovered in pineal glands. To date, the political and social implications of the power to change the color of skin have been less thoroughly explored.

Another remarkable disclosure is from Drs. Bondy and Cohn, who state that unconjugated etiocholanelone, an adrenal hormone, is present in the blood plasma of individuals during attacks of a mysterious disease called periodic fever, a recurrent illness chiefly of Sephardic Jews.

The problems of the thyroid and of its iodine-containing hormone have long held the interest of investigators at Yale. The late Dr. William Salter was a pioneer in the development of chemical methods for the study of this hormone. He introduced the use of radioactive iodine, which is concentrated in the gland, as a means of reducing its activity for the treatment of congestive failure of the heart. Two widely used methods for the detection of biologically significant iodine in the blood have been worked out largely through the efforts of Dr. Evelyn Man. The first method for "protein bound iodine" (PBI) has been replaced by the more recently developed method for "butyl extractable iodine" (BEI). These techniques have served as tools for the investigation and scientific treatment of thyroid disease by Dr. Peters and his staff, first with Lugol's solution and later with the thiourea derivatives.

NORMAL AND ATYPICAL GROWTH

Aspects of growth, normal and abnormal, have been approached at the biological as well as at the basic chemical level. Dr. Samuel Clark Harvey, surgeon and philosopher, made fundamental contributions to knowledge of factors in wound healing, using the tensile strength of the wound for a quantitative approach.

The importance of tissue transplantation has just been acknowledged in the award of the Nobel prizes for 1960. Basic contributions to transplantation technique and theory have come from the laboratory of Dr. Harry S. N. Greene who disclosed that embryonic tissues and certain malignant tumors, especially those with the capacity to matastasize, can be transplanted to the anterior chamber of the eye or to the brain of another species, while benign neoplasms fail. Transplanted undifferentiated tumors sometimes reveal their true nature or origin in the new host. The method can also be used

for growing in the transplants, agents of disease specific for the donor but harmless to the host. These studies have great theoretical as well as practical importance. World-wide attention has been drawn to Dr. L. S. Stone's studies of returning or altered vision in transplanted eye of the salamander.

The community of science suffered a great loss in the recent death of Dr. Francisco Duran-Reynals, one of the most active champions and brilliant investigators of the virus theory of cancer. He demonstrated the infectivity of the Rous virus, a filtrable agent that can produce tumors in fowl, in duck embryos or newly hatched ducklings; mature ducks appear to be immune.

In animals of low resistance the Rous virus produced lesions like those of an infection, while animals with high resistance developed tumors. At the time of his death he was applying the fruits of another great discovery, that of a tissue-spreading factor, hyaluronidase, to his work with cancer. At the present time the role of viruses in various forms of cancer in animals is becoming increasingly apparent, and there are hints of their existence in some human tumors.

GENETICS

For many years strains of inbred mice, with relatively constant characteristics, were developed and maintained at Yale by Dr. Leonell Strong and his associates. These have provided a powerful tool for investigating many aspects of neoplastic and other diseases. They served also to replenish stocks lost in the fire at Bar Harbor whence the ancestors of some of these animals had come.

Outstanding studies in genetics have been done at Yale by Drs. Tatum and Bonner and their associates who demonstrated the transmissibility of specific enzymic characteristics in fungi, and by Dr. Lederberg who is credited with the discovery of sex in bacteria among his other contributions. The importance of this work was acknowledged in the award of the Nobel prize to several members of the group which was shared with Professor Beadle the teacher of some of them.

POWER OF THE INVISIBLE RAYS

Work on biological effects of x-rays at a fundamental level was done in the Department of Pathology by Drs. Hussey and Thompson as early as the twenties. The rate of radiochemical inactivation of enzymes was studied under various experimental circumstances. The influence of the rays on the development of Drosophila larvae was investigated.

At Yale Dr. John H. Lawrence, a brother of the physicist and Nobel Laureate E. O. Lawrence, pioneered radioactive phosphorus in the treatment

of diseases of the blood, especially leukemia. He and Dr. Robert Tennant were among the first to make a biological comparison of x-rays and neutrons in mammals. The study of the leukemogenic action of radiation in relation to genetic and other factors was begun in New Haven by Dr. Henry S. Kaplan and has been brilliantly continued in his present post at Stanford.

CONGEALMENT AND SOLUTION OF THE BLOOD

How much suffering and death we could prevent if we fully knew what causes the blood to clot! Here outstanding contributions have been made by Dr. J. Haskell Milstone in his analysis of the clotting mechanism into three separate stages. The purification of the substance thrombokinase, responsible for the initiation of the first stage, and subsequently its characterization as a trypsin-like enzyme, represent an important achievement.

Of great interest is the purification and characterization of an anti-clotting agent, plasmin, by Dr. D. L. Kline and colleagues. Its possible application in the solution of clots within living animals is being investigated by Drs. Hume, Glenn, and associates.

VASCULAR DISEASE

Diseases of the blood vessels now represent the most important cause of death in America. When Dr. Winternitz relinquished his deanship, he returned to an early interest in vascular disease. Almost at once he made the noteworthy discovery that hemorrhage within the walls of vessels contributes to the development of arteriosclerosis, and also to coronary occlusion. In this process the vessels of the vessels, the vasa vasorum, were shown to be important. The observations were summarized in a book with Drs. Thomas and LeCompte *The biology of arteriosclerosis.* The relation of the kidney to cardiovascular disease was explored in an extensive series of experiments. These considered differences in the lesions when both renal arteries were ligated, as compared with those following ablation of the kidney, and also the pathology produced by injection of renal extracts.

Dr. L. L. Waters found that a simple chemical compound, allylamine, produced remarkable lesions of the vessels, particularly coronary arteries of the dog and this has been extensively studied together with other factors, such as blood lipids in the pathogenesis of vascular disease.

ELECTRICITY OF THE BODY

That every living thing has about it an electrical field was a discovery of immense significance. In the hands of the Dutch physiologist, Einthoven, it found its first important application in the electrocardiograph. The mechan-

ism of the electrocardiogram has been illuminated by the work of Drs. Hoff, Nahum, and their associates. They disclosed the dominant role of the surface layers of the heart in determining the character of the electrocardiogram and helped to establish the quantitative contribution of the two chambers. A study of chemical influences revealed involvement of adrenalin in the effects of benzol and certain other substances, and the importance of acetylcholine in the genesis of auricular fibrillation. An outstanding contribution is to the understanding of the effects of electrolytes, particularly potassium. Further basic work by Dr. Nahum has contributed to the understanding of unipolar electrocardiography. Electrocardiography has been applied also to the study of fetal distress by Drs. Hon and Hess.

A wider investigation of the electricity of the body has been made by Dr. Harold Burr who has studied electrical fields related to various cyclical events such as ovulation, and the electrical correlates of growing cancer and even of growing plants.

STORMING THE BASTIONS OF THE BODY

One by one the formerly inaccessible fortresses of the body have been stormed. Access can now be readily obtained to the central nervous system, the contents of the chest, and even to the interior of the heart itself.

Free entry into the thorax was not possible until the development of technical methods, of which the most important was positive pressure anesthesia. To this both Drs. Joseph Marshall Flint and Herbert Thoms made a contribution. One of the most original discoveries in pulmonary physiology is that of collateral respiration—the demonstration of a "back door" to the distal air spaces—by Drs. van Allen and Lindskog. Dr. Lindskog also contributed the method of resection for lung abscess. Some of the earliest experimental observations on the collateral circulation were made by Dr. Schlaepfer in the twenties. More recently the expansion of the collateral circulation in disease, its effect on the shunting of blood, and its possible application as a means of building vascular bridges to the coronary arteries have been explored in a joint effort between Pathology and Surgery.

One of the first applications of surgery to cardiac problems was the development of pericardiolysis by Drs. Marvin and Harvey as early as 1924. By this technique the heart is freed from an adherent constricting thickened pericardial sac. An early cardiac pump was developed by Dr. William Sewell while still a medical student working with Dr. Glenn. Dr. Glenn devised also the ingenious procedure of sewing an artificial pouch to the heart through which structures in the interior can be approached and repaired. A major advance made by Drs. Glenn and Patiño is that of "right

heart bypass," a method of circumventing a deformed or incompetent right cardiac chamber by directly connecting the superior vena cava with the pulmonary artery. This method has now proved its usefulness in tricuspid stenosis and its utility in other conditions is under study.

Although man early in his history dared, by trephination, to enter the skull with therapeutic intent, the workings of its contents are still largely unknown. At Yale the functions of the frontal lobes have been explored by application of experimental brain surgery in higher apes, coupled with psychobiological training techniques. An outstanding achievement was the investigation of the effects of lobotomy by Drs. Fulton and Carlyle Jacobsen. As a result of this procedure, two anxious and temperamental chimpanzees, Becky and Lucy, were transformed to a commendable state of calmness and apparent rationality. This finding, reported at a Congress in London and also in Moscow in 1935, suggested a procedure for alleviating certain mental disorders in man, and this was first accomplished by Egas Moniz in Portugal. Dr. Fulton has been acclaimed the father of lobotomy, but he always modestly said that if he were the father, it was a case of unplanned parenthood.

The seat of the soul, if it is indeed in the brain, has not as yet been discovered, but the seat of a less noble property, the appetite, was discovered in New Haven. Dr. Brobeck, at various times in association with Drs. Tepperman and Delgado, found that injury to certain deeply lying centers in the hypothalamus led to an enormous increase in appetite, whereas injury to others nearby led to total anorexia. The psychological aspects of such changes in appetite have attracted the study of Dr. Neal Miller of the Department of Psychology.

That ancient portion of the brain which in higher forms is dominated and obscured by the greatly expanded cerebral cortex, has been brilliantly illuminated by Dr. Paul MacLean and his associates. He has called this limbic system the "visceral brain" to indicate its function as a major center for the correlation of every form of internal and external perception—what we "feel" as contrasted with what we "know". The latter function appears to be served by the outer mantle of the brain, the neopallium which reaches its highest development in man. The limbic system has been further explored by Delgado with the use of multiple electrodes through which stimulation or coagulation can be brought about. This system has been found to influence many phases of autonomic function such as the sexual, as well as patterns of emotional behavior. The limbic system has thus emerged as a distinct functional entity.

A method for stimulating portions of the brain in fully conscious animals by means of previously implanted electrodes was used as early as the thirties

by Dr. Richard Light of the Department of Surgery. In an extensive new development by Dr. Delgado it has been used not only in exploration of the limbic system but also in the study of the cerebral cortex in its various layers, as well as regions, and the work has been extended to man. At long last man's ancient interest in phrenology has been converted to a science.

MAN AND MIND

The idea so clearly conceived by Dr. Winternitz, that man is mind as well as body, and that he cannot be considered apart from the society in which he lives, led to the creation of the Institute of Human Relations and to the world-wide search for outstanding leaders in psychiatry. Numerous devoted efforts for the solution of problems falling into this sphere have been exerted but no more than a few can be mentioned: the dynamics of humor in relation to mental disorders (Drs. Levine, Redlich, Laffal, *et al.*) ; the interaction of the schizophrenic patient with his family (Dr. Lidz). Some extensive investigations have formed the basis of published volumes: *The initial interview in psychiatric practice* (Drs. Gill, Newman, Redlich, and Margaret Sommers) in the course of which recording techniques were developed and extensively applied; *Social class and mental illness,* an interdisciplinary study by Profs. Hollinshead and Redlich. Psychological studies of lobectomized patients have been made by Dr. Brody.

The inseparability of mind and matter has been recognized: Dr. Daniel Freedman, after training at the National Institutes of Health, has established a laboratory of Psychopharmacology in collaboration with Dr. Giarman, Professor of Pharmacology. Drs. MacLean and Delgado have held joint appointments with physiology.

It was in the hope of obtaining a better understanding of man, that primate biology and psychobiology were extensively developed by Dr. Robert M. Yerkes in the colonies at New Haven and at Orange Park, Florida. Such topics as intelligence, comparative psychology and psychopathology, social behavior, mother-infant relationships, received special attention, especially in anthropoids. Opportunities were also seized for investigating the somatic sphere such as the chromosomes and reproductive cycles. Two classic volumes were published: "The Great Apes" (1929) and "Chimpanzees" (1944). New interest is manifest now in the support of several "primate centers" in this country by the Public Health Service.

CARE OF MOTHER AND CHILD

The poet said "The child is father of the man." Nowhere in this country has the understanding of the mother and of the physical and mental nurture

of the child been better served than at Yale. Dr. Thoms' new method of x-ray pelvimetry made possible the accurate measurement and classification of that "graceful arch 'neath which the noblest heads have passed." Under Dr. Donald Barron there have flourished studies of prenatal life which he had begun at Cambridge as a student, and later collaborator of Barcroft. Dr. Barron's recent researches have contributed to the elucidation of how oxygen, the breath of life, and other nutrients are transferred across the placenta and how these are used in the growth of the fetus. In this work various barriers have been broken. His associates have come from other Departments and even from other Universities, Boston, Harvard, and Johns Hopkins. Recently this work has brought him and his associates to the peaks of the Andes where the problems of the fetus are immensely magnified by the rarified atmosphere.

In her intensive observations over a long period of years Dr. Gertrude van Wagenen has provided valuable data on the sexual cycles, response to hormones, gestation and birth in a primate species, the macaque.

Dr. Edward Hon combined his expert knowledge of obstetrics and electronics to develop with Dr. Orvan Hess, an early warning method to detect fetal distress. One principle early employed by them was to record the fetal electrocardiogram apart from that of the mother and to subtract by electronic means the latter from that of the fetus. More recently the procedure has been simplified.

The Read method of "natural childbirth" was introduced into this country at the New Haven Hospital largely through the influence of Dr. Herbert Thoms and "rooming-in" was born in New Haven. This scheme of caring for the mother and her newborn infant together in the same unit of space, was initiated through the interest of Drs. Powers in Pediatrics, Morse and Thoms in Obstetrics, and Dr. Edith Banfield Jackson who directed the project with such able assistants as Drs. Olmstead and Ethylyn Klatskin. The cooperation of the administrative staff of the hospital was granted, with some misgivings, by Dr. Snoke. The term rooming-in came into general use with its theoretical description in the book *Infant and child in the culture of today* by Drs. Gesell and Ilg. The "rooming-in" principle is now widely used in many institutions.

The principles of infant nutrition were clarified by Dr. Grover Powers and his group who emphasized the total caloric intake of a suitable mixture of proteins, fats, and carbohydrates, with vitamin supplement. A successful regimen for premature infants was worked out which has been of incalculable benefit. The massive problem of rickets was attacked and the importance of sunlight in its prophylaxis and therapy was demonstrated. Studies

of vitamins also were a long and important preoccupation of the Pediatric Clinic.

The Yale Clinic of Child Development has exerted a profound influence on the life of the civilized world. From its modest beginnings in 1911, it came to full bloom in the early thirties in its magnificent quarters in the Sterling Hall of Medicine. "Gesell" became a household word as volume after volume appeared describing the norms of development as observed by painstaking cinematographic and other methods by Dr. Gesell and his associates, Drs. Thompson, Amatruda, Ilg, Ames, and others.

Those who have brought up children "according to Spock" also have not escaped a touch of the Yale spirit since this eminent pediatrician received his medical degree in this city.

New approaches have been made under Doctor M. J. E. Senn, the present Director of the Clinic, who has emphasized the understanding of the child within the background of his family.

BATTLE OF THE MICROBES

In the struggle against pestilence, men of Yale have struck valiant blows. Dr. Francis Blake who had been brought to New Haven by Dean Winternitz as Professor of Medicine, had been a member of the Army Pneumonia Commission during World War I, and had worked for an additional 20 months of post-war service at the Army Medical School in company with Dr. Russell L. Cecil. Together they produced a series of classical papers on the pathogenesis of pneumonia. With this experience behind him, his interest in the disease was maintained and he, in collaboration with Dr. James D. Trask, made early disclosures on the development of variants of the pneumococcus, particularly the production of the "rough" unencapsulated form by growing the "smooth" forms in immune serum. Another contribution was the introduction of pneumothorax to relieve discomfort and dyspnea in the acute phases of the disease.

In the 1920's scarlet fever was a dread disease with a high mortality. Following the discovery by Dochez that the disease was caused by a toxigenic hemolytic streptococcus, the toxin was demonstrated in the blood and urine of patients. Drs. Blake and Trask moreover were able to show the effectiveness of an antitoxic serum.

Concurrently another disease thought to be of streptococcal origin, rheumatic fever, was being intensively investigated by Dr. John R. Paul. The spread of the disease was studied within families as a clue to the more general problem of its transmission. Such "family epidemiology" he applied subsequently with notable success in the study of poliomyelitis, and it has

been widely used by others in the investigation of infectious disease. What is now known as the Paul-Bunnell test for infectious mononucleosis was in fact a by-product of these studies—an example of serendipity which in Dr. Greene's paraphrase is the "finding of farmers' daughters while searching for a needle in the haystack." There seemed to be some similarities between rheumatic fever and the serum sickness which followed the administration of horse serum then being used extensively in therapy. It had been discovered that the plasma of persons with serum sickness had the remarkable property of causing the red blood corpuscles of a foreign species such as the sheep to agglutinate—as if the person had been previously injected with them. Substances responsible for this phenomenon were called heterophile antibodies. This led Dr. Paul and his associate Dr. Bunnell to investigate the blood of persons with rheumatic fever together with "controls" suffering from a large variety of other conditions, for such antibodies. It was found that individuals of the "control group" with infectious mononucleosis had the highest concentration of antibodies and this has subsequently been used as a test for the disease. As a historical aside it is interesting that the first patient in the series was a medical student who is now the Connecticut State Commissioner of Health.

In 1931 the Yale Poliomyelitis Unit was founded. From its beginning with the collaboration of Drs. Trask and Paul it has been carrying on outstanding work to this day. No less than 6 of the 17 members of the "Polio Hall of Fame" have at one time or another worked in the Unit. An immediate contribution resulting from the application of the technique of "family epidemiology," was the demonstration of virus in the throats of persons with nonparalytic disease during epidemics of the paralytic form. Within two years it was disclosed that there was more than one type of polio virus. Of major importance in understanding the dissemination of the disease was the discovery of the virus in intestinal contents of patients, in sewage at the time of greatest prevalence of the disease, and in flies obtained from the near vicinity of houses harboring infected persons. Remarkable investigations in what may be called "serological epidemiology" were begun in 1943 when poliomyelitis was found to occur frequently in soldiers in North Africa. It was then observed that practically all adult natives in this region carried antibodies in the blood—having apparently been immunized much earlier in life in consequence of the great prevalence of the infectious agent. Paradoxically, high standards of cleanliness appear to decrease the immunity of a population. This is a general principle of epidemiology in the tropics, that has been demonstrated with reference to diphtheria as well as to poliomyelitis: crowding and filthy conditions of life make for universal infection

and only those that acquire immunity survive. The presence of immune bodies could also be used to establish the occurrence of infection in years past, as was demonstrated among the Eskimos in such regions as Point Barrow, Alaska. In the 1940's came the discovery of the Coxsackie group of viruses. Subsequently Dr. Melnick and his collaborators in the Unit were in the forefront in classifying this large family of agents and in studying the diseases produced by them. In 1950 Dr. Dorothy Horstmann demonstrated poliomyelitis virus in the blood early in this disease, thereby illuminating its method of spread through the body, a fact established almost simultaneously by Dr. Bodian at Johns Hopkins. In the 30 years of the existence of the Poliomyelitis Study Unit more than 325 papers have been published, an indication of the activity of this group. Currently, work is progressing apace in the study of the live poliomyelitis vaccines.

As early as the nineteen twenties hepatitis was a subject of study in New Haven. It was then that Dr. George Blumer wrote of his conviction that catarrhal jaundice was a sporadic form of epidemic hepatitis, but this was not generally accepted for 20 years. During World War II Dr. Paul Havens then at work in New Haven made important contributions to the differentiation of infectious hepatitis and serum hepatitis, a clinically similar disease transmitted by contact with infected blood as in transfusions, or even by needle punctures. He also demonstrated that infectious hepatitis could be transferred from man to man by feeding the virus. In the hands of Dr. Gerald Klatskin the liver biopsy method has yielded significant information on the natural history of hepatitis and of granulomatous and other diseases of the liver.

Infections of the kidney, pyelonephritis, were studied by Dr. John Peters and Dr. Zimmerman who emphasized the frequency of the condition in pregnancy and its relation to the subsequent development of high blood pressure. Within the past few years noteworthy contributions to the study of this disease have been made by Dr. Paul Beeson and his associates, chiefly Drs. Lawrence Freedman, Rocha, and Guzé. They have concerned themselves with the peculiar susceptibility of the kidney to infection with coliform bacilli. While on a working sabbatical in England, Dr. Beeson with Dr. Rowley reported that kidney tissue interferes with the bactericidal action of blood serum for these organisms. This activity is 5-15 times greater than that of other tissues, and is exerted on the fourth component of complement, that which is characterized by susceptibility to injury by ammonia. Phosphate and glutamine which favor ammonia formation, enhance the anticomplementary activity of renal homogenates.

Infection with a new species of Listerella was reported by Dr. C. G. Burn.

Serious attention has been paid to the important subject of the bacterial toxins. The most highly purified preparation of diphtheria toxin available to that time was prepared by Drs. Bayne-Jones and Eaton and its properties revealed. The spread of tetanus toxin along nerves in the pathogenesis of tetanus was also investigated by the former. Immunity in tetanus, with special reference to the toxoid, was studied by Dr. P. B. Cowles.

The economy of state and country was handsomely served by another bacteriologist, Dr. Leo F. Rettger, through his work on the destructive Salmonella-induced diarrhea of chickens, and on infectious abortion in cattle. He contributed also new information on the intestinal flora especially on the effects of the *Lactobacillus acidophilus.*

In February, 1944, Yale University was presented with a collection of over 300 chemical products that had been isolated from the tubercle bacillus. This, the work of Dr. Rudolph J. Anderson and his associates, represents the most complete chemical dissection of an organism ever made. It was begun in 1926 when Dr. Anderson came to Yale at the invitation of Professor Treat B. Johnson, who had already been working with nucleic acids and proteins of this species. The effects of many of these substances in animals were studied by Dr. Florence R. Sabin at the Rockefeller Institute. Dr. Anderson's work was one of the first demonstrations of the value of long term grants, in this case from the National Tuberculosis Association.

With the new era of effective chemotherapy in infectious disease there arose new opportunities and problems. Dr. Francis Blake with such associates as Hageman, Haviland and Sadusk were able to make significant contributions regarding the absorption, excretion, dangers and most effective clinical use of the sulfonamides. In June of 1941 Dr. Francis Blake had an earnest conversation with Prof. Howard Florey and six months later gave the first dose of penicillin in this country to a patient with post-abortal streptococcal infection from which she then miraculously recovered. Dr. Beeson and his staff have carried forward this tradition of intensive study of chemotherapeutic agents and have joined with Dr. Welch in planning a special unit for the intensive study of these substances in infectious disease, cancer and other conditions.

ANIMAL HEAT

Fever is a frequent accompaniment of infectious and some other diseases and the effects of substances which control it, the antipyretics, have been of interest to physicians throughout the ages. Significant physiological studies were done by Dr. Barbour who demonstrated the importance of water transfer, and of the nervous system in the control of cutaneous circulation. More

recently Drs. Beeson and Ivan Bennett have investigated the properties of pyrogens in bacteria. They have also found a pyrogenic material in white blood cells. Dr. Elisha Atkins, pursuing another facet made the important disclosure that pyrogens, made by the body, can appear secondarily after injection of exogenous pyrogens such as bacteria or even certain viruses. The role of etiocholanelone in "periodic fever" has already been mentioned.

HEALTH OF THE PEOPLE

There has been a great tradition in Public Health at Yale succinctly phrased in Professor Winslow's credo: "Within natural limitations a community can determine its own death rate." Work toward this end consisted, in part, in the development of standards for health organizations. Techniques of community health surveys were developed, an activity in which Professor Hiscock played a large and direct role. Such cities as Boston, Pittsburgh, Cleveland, Minneapolis, Kansas City, San Francisco, and Los Angeles were actually surveyed. The standards established have been almost universally accepted as the basis for community health programs. Studies in industrial hygiene begun by Dr. Leonard Greenburg have been continued by Dr. Wister Meigs who has investigated such industrial problems as that of carbon monoxide poisoning. In the J. B. Pierce Laboratory of Hygiene, fundamental physical and physiological studies of the relation of environment to comfort and survival have been made. Socioeconomic factors in cancer have been extensively investigated by Dr. Cohart. The abiding interest of the Department in more local affairs has been expressed in housing within New Haven and in the founding and support of the Connecticut State Department of Health.

DENTAL RESEARCH AT YALE

Although there has never been a school of dentistry at Yale, there has been much interest in dental research fostered especially by Dr. M. C. Winternitz and led for many years by Dr. Bert G. Anderson. During its most active years, in the middle thirties, the Dental Research Unit was supported largely by the Rockefeller Foundation and obtained its recruits from among outstanding graduates of dental schools who then took additional work at Yale towards the M.D. degree, while participating actively in investigative work. Collaboration and supervision were obtained from men in several departments of the School of Medicine, among whom Dr. C. G. Burn was most active. The accomplishments of this group were solid. Dental caries, periapical infection, the role of hypersensitivity in localizing infection, enamel formation, and changes in congenital syphilis

and from excess of fluoride, were among the many subjects of study. Remarkable adamantinomatoid proliferations were discovered in animals with vitamin A deficiency. Many of the men trained in this unit have gone on to positions of leadership in dental education and research elsewhere.

YALE MEDICINE IN WARTIME

In time of war a great University and a great Medical School may be assets more valuable to a nation than an army or fleet. In those times of stress Yale has abundantly given of herself both at home, and closer to the battle. It is to be expected that senior professors should be called upon to direct such affairs as those of the National Research Council, as was Professor Ross Harrison in World War II; of the Army Epidemiological Board as was Dr. Francis Blake; and of the medical work of the Chemical Warfare Service as was Dr. Winternitz. These represent a very few of the many services thus rendered.

In World War I Dr. Winternitz, as well as Dr. Underhill, had much to do with the investigation of the biological effects of war gases, and he published a classical monograph on the subject. When the first World War ended, the CWS laboratories were flourishing, but when World War II began he complained that all he found was a "desiccated kernel." From this humble beginning came the medical laboratories of the Army Chemical Center at the Edgewood Arsenal. An important result for civilian medicine was the discovery by Dr. Alfred Z. Gilman and associates that the nitrogen mustards could inhibit the multiplication of cells. This has found application in the treatment of cancers and leukemias.

Yale has been closely associated with aeromedical research from its beginnings. Early in the century Professor Yandell Henderson engaged in high altitude investigations with particular reference to anoxia, and during that war he became the Chairman of the first Committee on Aviation Medicine to be formed in this country. In the course of World War II a large decompression chamber was installed at the Sterling Hall of Medicine. Here were done important studies on anoxia, shock, and adrenal mechanisms. Outstanding contributions in the Yale Aeromedical Unit were those of Dr. Walter Miles of the red dark adaptation goggle, and of a practical G-suit by Dr. Lamport. Both items received important applications in action.

In both World Wars hospital units were organized at Yale, each time designated "The 39th." In World War I a major contribution was that of the Mobile Surgical Unit, a concept brought to our Army for the first time by Dr. Flint, who had previously studied it intensively among the French. This led to the development of mobile units of all types in World War II. In

the Second World War the Yale Unit in the Pacific contributed the discovery that the widely prevalent and disabling form of "jungle-rot" was in fact caused by diphtheria bacilli, which then produced epidemics of the common throat disease among susceptible soldiers. Natives of the tropics except for a brief period between nine months and two years, were found to be immune, again demonstrating the general epidemiological principle of immunity in the tropics that was well studied in relation to poliomyelitis. The epidemiology and natural history of hookworm disease were also investigated. A species of diphtheria-like bacillus hitherto undescribed also was discovered as a common organism in the respiratory tracts and skin infections of men in the tropics.

The investigation of the atomic bomb casualties in Japan was led by the late Dr. A. W. Oughterson, who had been Surgical Consultant to General MacArthur. Four of the seven Medical Officers who carried out the study at Hiroshima had been members of the Yale Unit, or had received their medical degrees in New Haven. Their work, published as a monograph, represents the only definitive report of the subject.

It may be asked what is the place of research in an institution that is a *school* of medicine. Surely the concept of the "trade school" dissolves as it becomes more widely understood that the quality of the scholarship needed to learn how a cell grows in the milieu of the living body, may not be less than that required to annotate creatively the papers of a great man in the framework of his time. Surely the natural home of scholarship in medicine is the university which leavens it, and which is in turn leavened. No physician is better than his science and his humanity, and his science is no better than the research which gives it nourishment. A school devoted to research is preoccupied with the process of *learning*—a preoccupation which after all means the best teaching. At this school every student must have an experience in research before the degree Doctor of Medicine is awarded. Research at Yale is an attitude of mind that precludes the cessation of learning—a continuing adventure in which the young may join older colleagues in the exploration of the unknown and in the hopes of achieving, in the clinic as in the laboratory, an ever improving understanding of man and nature.

A documented account, hopefully worthier of the subject and with fewer omissions of important work, will be published as a chapter in the Sesquicentennial Commemorative Volume.